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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,928	05/09/2005	Ralph Patrick Braun	HO-P03173US0	6804

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,928	BRAUN ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 28-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 and 28-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 1-25 and 27 have been cancelled. Claims 26 and 45 have been amended.

Claims 26 and 28-49 are pending and under examination.

Response to Arguments

Specification

3. The objection to the specification is withdrawn in response to Applicant's amendment to include cross-reference to the priority documents. The amendment was filed on 05/15/2008.

Double Patenting

4. The provisional obviousness-type double patenting rejection of claims 26, 28-34, 37-39, and 40-42 as being unpatentable over claims 1, 2 and 9-15 of copending Application No. 10/380,981, in view of Kotsopoulou et al. (J. Virol., 2000, 74: 4839-4952) is withdrawn because Application No. 10/380,981 has been abandoned in favor of a continuation application, Application No. 11/764,814.

However, since the claims of Application No. 11/764,814 are identical to the claims of the abandoned Application No. 10/380,981, the double patenting rejection is repeated as follows:

Claims 26, 28-34, 37-39, and 40-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 9-15 of copending Application No. 11/764,814, in view of Kotsopoulou et al. (J. Virol., 2000, 74: 4839-4952). The claims are rejections for the reasons of record set forth in the non-final Office action of 11/15/2007.

Applicant has requested that the obvious-type double patenting rejections set forth by the Examiner be held in abeyance. The Applicants' comments are acknowledged, however the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

5. Claims 26, 28-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 7-11 of copending Application No. 10/508,143, in view of each Woodberry et al. (J. Virol., 1999, 73: 5320-5325) and Kotsopoulou et al. (J. Virol., 2000, 74: 4839-4952) for the reasons of record set forth in the non-final Office action of 11/15/2007.

Applicant has requested that the obvious-type double patenting rejections set forth by the Examiner be held in abeyance. The Applicants' comments are acknowledged, however the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The rejection of claims 26 and 45 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendment to the claim filed on 05/15/2008.

Applicant notes that claim 26 is listed as being rejected on Page 9 of the non-final Office action of 11/15/2007. Applicant argues that claim 26 lacks the element of a heterologous promoter comprising exon 1 and requests clarification of this issue. In response to this argument, it is noted that claim 45 is currently amended to depend from claim 44. At the time the rejection, claim 45 was directly dependent on claim 26, and therefore, claim 26 encompassed the embodiment under rejection.

Claim Rejections - 35 USC § 103

7. Claims 26, 28, 29, 36-38, 42, and 47-49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodberry et al. (J. Virol., 1999, 73: 5320-5325), in view of each Peter et al. (Vaccine, 2001:19: 4121-4129, Abstract), Goulder et al. (Immunol. Lett., 2001, 79: 109-116, Abstract), and Miller et al. (WO 93/20847) for the reasons of record set forth in the non-final Office action of 11/15/2007. Applicant's arguments filed 05/15/2008 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the Examiner provides no reference which teaches the 12 to 36 hour administration of imiquimod as is recited in the instant invention. The Examiner's rejection is based on the assumption

that it would have been obvious to one of ordinary skill in the art to vary the parameters in the method with the purpose of optimizing the results and that such conditions can be identified by routine experimentation. However, this is not the case, Applicant requests that the Examiner find support for the assumption with adequate evidence (MPEP § 2144.03 C). The requirement for the imidazo compound to be administered 12 to 36 hours after the vaccine is an aspect of the instant invention. This is illustrated by the Examples in the application. The Examiner made the rejection "[a]bsent evidence of unexpected results" (the Action, page 11), but the Examples provide such evidence. Applicant points to Examples 1, 2 and 7 in the specification, wherein the exemplary results show that administration of the imidazo compound one day after immunization with the vaccine gave a significant immune response (see especially Table 1 on Page 83 and Figure 16). Although Applicants asserts that the use of the 12 to 36 hour time window specified in the claims was not obvious from the combined teachings of Miller, Woodberry, Peter and Goulder, solely to further prosecution of this case, Applicants clarify the claims by amending claim 26 to recite that the compound is administered only 12 to 36 hours after the nucleic acid vaccine is administered. Applicant points out that none of the references disclose or suggest that administration regimen for that time window; the fact that the present Examples demonstrate that such an advantage exists was entirely unpredictable from the references. Further, the amendment to claim 26 clarifies that the imidazo compound is not given simultaneously with the vaccine, but is only administered within the window of 12-36 hours after the initial vaccine was given. Applicant submits that the only reference which contains any teaching that is even

remotely relevant to the time window required by the present claims is Miller; however, Miller merely contains a generic disclosure that the imidazo compound should be administered simultaneously or after (e.g. 48 hours after) immunization with the vaccine (see especially page 15, lines 17-30 and page 28, lines 1-21). Applicant argues that Miller does not disclose the sole and specific time window of 12 to 36 hours required by the present claims or suggest that there would be any advantage in using this time window in addition to Applicants' claimed administration regimen. Additionally, Applicant argues, the administration regimen used by Miller teaches away from the instant invention. Miller teaches using 5 mg/kg/day for five consecutive days starting either concurrently with or 48 hours after vaccination (Miller, page 28, lines 1-12), i.e., Miller teaches administration over the course of five days for therapeutic effectiveness of the adjuvant. The claims herein recite the use of only the specific 12 and 36 hours after vaccination. Further, Example 1 and Figure 1 of the Specification show that administration of the adjuvant only in the 12 to 36 hour time window is superior to administration daily for three days on days 0, 1 and 2, in one embodiment of the invention. This result is unexpected given the disclosure of Miller. Applicant submits that the Examiner did not establish a *prima facie* case of obviousness and did not identify the reason that would have prompted one of skill in the art to combine the references given the instant invention. As Miller teaches away from the invention by teaching administration over the course of five consecutive days, as opposed to administration only in a certain time window, one of skill in the art would not use the combination of Miller and Woodberry to develop the instant invention. Applicant

continues arguing that the Examiner made subsidiary rejections under 35 USC 103 that focused on dependent claims. Those rejections are unfounded for the reasons given above; all the dependent claims incorporate the subject matter of claim 26 and therefore set forth unobvious subject matter for at least the reasons given above. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant argues that the statement of optimizing the results by routine experimentation is not proper because the Examiner provides no reference teaching the 12 to 36 hour administration window for imiquimod. In response to this argument, it is noted that the Examiner does not need to provide such references, because the facts asserted to be known (in the instant case, optimizing the time of imiquimod administration) are capable of instant and unquestionable demonstration as being well-known (see MPEP 2144.03). In addition, MPEP 2144.03 states:

> "In appropriate circumstance, it might not be unreasonable to take official notice of the fact that it is desirable to make something faster, cheaper, better, or stronger without the specific support of documentary evidence";

The Examiner stated that, absent evidence of unexpected results, it would have been obvious to one of skill in the art to test different times for imiquimod administration with the purpose of optimizing the results; the Examiner also stated that this could be achieved by routine experimentation. MPEP (2144.05 [R-3] II) states that, if a parameter is recognized as a result-effective variable, such variable might be characterized as routine experimentation. In the instant case Miller et al. (WO

93/20847) teach administering imiquimod for five consecutive days starting either concurrently with or 48 hours after vaccination. Additionally, Miller et al. (Int. J. Immunopharmacol., 1999, 21: 1-14, Applicant's IDS) teach applying imiquimod between 72h before and 24h after nucleic acid administration (p. 3, last paragraph). Therefore, the art teaches varying the administration time to optimize the results (i.e., the art recognizes the time of imiquimod administration as result-effective variable); it is noted that the 24h time point (i.e., between 12 and 36h) is specifically disclosed by the prior art, and therefore, Applicant's argument of unexpected results is not found persuasive. Based on the teachings in the art as a whole, it would have been obvious to one of skill in the art to use routine experimentation to optimize the time of imiquimod administration; additionally, one of skill in the art would have been aware of the 24h time point as adequate for inducing a strong immune response. The argument that the specification provides evidence of unexpected results is again not found persuasive. Example 1 and Fig. 1 disclose administering 1 μg or 50 ng vaccine followed by imiquimod at different time points; four mice were used for each time point. While imiquimod administration 24h after vaccination results in a somewhat higher immune response when 1 μg vaccine was administered, this is not the case when the lower dose of 50 ng vaccine is administered; for lower nucleic acid dose, the immune response is basically the same, regardless of when imiquimod administration occurred (see Fig. 1). Additionally, Example 1 clearly teaches that the higher immune response obtained at 24h with 1 μg vaccine is due to two strong responder mice and not to the fact that imiquimod was administered 24h post-vaccination (see p. 77, lines 21-30).

Example 2 and Table I only show the results obtained at day 0 and 24h post-vaccination; there is no comparison with other time points (see also Fig. 4). Fig. 16 only shows the results obtained with imiquimod administration before, right after, and 24h post-vaccination; there is no comparison with later time points. Example 7 clearly discloses that delivering imiquimod at any time point between 1 day and 7 days is equally effective (i.e., later time points which do not appear in Example 2, Table 1, or Fig. 16) (p. 80, lines 20-31, p. 82, lines 28-30). Based on these teachings in the specification, one of skill in the art would not recognize that the use of the specific window of 12-36h results in unexpected results when compared to later times, which later times are taught by the prior art. Specifically, the specification teaches that later times up to 7 days post-vaccination are equally effective. Therefore, there is no evidence of unexpected results when using the window of 12-36 h. Moreover, as noted above, the time point of 24h is already taught by the prior art. Because, for the reasons set forth above, it would have been obvious to one of skill in the art to optimize the results, it is concluded that Miller et al. do not teach away from the instant invention and the rejection is maintained.

8. Claims 26, 28, 29, 36-43, and 46-49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodberry et al. taken with Peter et al., Goulder et al., and Miller et al., in further view of both Zhang et al. (Immunol. Lett., 2001, 79: 93-96) and Kotsopoulou et al. (J. Virol., 2000, 74: 4839-4952) for the reasons of record set forth in

the non-final Office action of 11/15/2007. Applicant's arguments filed 05/15/2008 have been fully considered but they are not persuasive.

Applicant argues that, while the Examiner uses Zhang as teaching p24 and Kotsopoulou as teaching codon optimized Gag and Pol, claims 26, 28, 29, 36, 37, 42, and 49 lack either element mentioned by the Examiner and provided in the additional Zhang and Kotsopoulou references and are thus, improperly included in this section. Additionally, Applicant argues, Zheng and Kotsopoulou, do not teach or suggest each element of amended independent claim 26. Specifically, none of the cited references teaches the 12-36 hour time frame and administration regimen for administration of the adjuvant. As all other rejected claims depend from independent claim 26, each dependent claim contains all the limitations of the independent claim. Thus, Applicant argues, a *prima facie* case of obviousness has not been established for any of the rejected claims and the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Claims 26, 28, 29, 36, 37, 42, 46, and 49 were properly included in the instant rejection because claims 39-41, 43, and 46 directly or indirectly depend from claim 26; therefore, claim 26 and all claims depending from it encompass the embodiments under rejection. With respect to the argument that none of the cited references teaches the 12-36 hour time frame and administration regimen for administration of the adjuvant, see above.

9. Claims 26, 28-35, 36-38, 42, and 47-49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodberry et al. taken with Peter et al., Goulder et al., and Miller et al., in further view of both Fynan et al. (Proc. Natl. Acad. Sci .USA, 1993, 90: 11478-11482) and Spruance et al. (The Journal of Infectious Disease, 2001, 184: 196-200; Applicant's IDS) for the reasons of record set forth in the non-final Office action of 11/15/2007. Applicant's arguments filed 05/15/2008 have been fully considered but they are not persuasive.

Applicant argues that, while the Examiner uses the additions of Fynan to teach the use of a gene gun and Spruance to teach the administration of a gel, claims 26, 28, 29, 36-38, 42, and 47-49 lack either additional element mentioned by the Examiner and provided in the additional Fynan and Spruance references and are thus, improperly included in this section. Additionally, applicant argues, the references cited, now including Fynan and Spruance, do not teach or suggest each element of independent claim 26. Specifically, none of the cited references teach or suggest only administration in the 12-36 hour timeframe for administration of the adjuvant. As all other rejected claims depend from independent claim 26, each dependent claim contains all the limitations of the independent claim. Thus, a *prima facie* case of obviousness has not been established for any of the rejected claims. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Claims 26, 28, 29, 36-38, 42, and 47-49 were properly included in the instant rejection because claims 30-35 directly or indirectly depend from claim 26; therefore, claim 26 and all claims depending from it encompass the embodiments under rejection. With respect to the argument that none of the cited references teaches the 12-36 hour time frame and administration regimen for administration of the adjuvant, see above.

10. Claims 26, 28, 29, 36-38, 42, 44, 45, and 47-49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodberry et al. taken with Peter et al., Goulder et al., and Miller et al., in further view of Mikkelsen et al. (Transgenic Research, 1992, 1: 164-169) for the reasons of record set forth in the non-final Office action of 11/15/2007. Applicant's arguments filed 05/15/2008 have been fully considered but they are not persuasive.

Applicant argues that, while the Examiner uses the addition of Mikkelsen to teach the use of HCMV IE-1 to drive gene expression, claims 26, 28, 29, 36-38, 42, and 47-49 lack the additional element mentioned by the Examiner and provided in the additional Mikkelsen reference and are thus, improperly included in this section. Additionally, Applicant argues, the references cited, now including Mikkelsen, do not teach or suggest each element of independent claim 26. Specifically, none of the cited references teaches only administration within the 12-36 hour time frame for administration of the adjuvant. As all other rejected claims depend from independent claim 26, each dependent claim contains all the limitations of the independent claim.

Thus, a *prima facie* case of obviousness has not been established for any of the rejected claims and Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Claims 26, 28, 29, 36-38, 42, and 47-49 were properly included in the instant rejection because claims 44 and 45 directly or indirectly depend from claim 26; therefore, claim 26 and all claims depending from it encompass the embodiments under rejection. With respect to the argument that none of the cited references teaches the 12-36 hour time frame and administration regimen for administration of the adjuvant, see above.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph T. Woitach/

Supervisory Patent Examiner, Art Unit 1633